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Dexmethylphenidate: A Viewpoint

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For a century it has been known that some drugs and naturally occurring physiological molecules (e.g. hexose, amino acids) occur in stereoisomers, with a right- and left-hand orientation. Some of these, in solution, have the property of deflecting light to the right or left and are also called optical isomers, designated as dextro- and levo- isomers. Not all stereoisomers are optical. Other types of stereoisomers include erythro- versus threo- and *cis* versus *trans*. Most naturally occurring molecules are all one isomer (e.g. all levo). But synthetic molecules (drugs) are made in approximately equal proportions of each isomer and require separation if only one isomer is desired.

It has also been known for decades that there are subtle differences between drug isomers in action. This offers the possibility of 'chiral pharmacology'. As early as the 1930s amphetamine was available as the racemic mixture, marketed as Benzedrine[®] and as the dextro-isomer, marketed as Dexedrine[®]. The levo- isomer was briefly marketed as Cydril[®]. Recently there has been an upsurge of interest in the possibilities of chiral pharmacology, driven partly by commercial incentive for patentable products as patents expire on racemic drugs. This interest has resulted in several contributions to the range of pharmacological options. Dexmethylphenidate is one of those.

Methylphenidate actually has four isomers: dextro- and levo- crossed with erythro- and threo-. Erythromethylphenidate was never marketed. Threomethylphenidate was marketed for 40 years as Ritalin[®]. Only in the past decade or so was the technology developed for economically separating out dextro-threo-methylphenidate, or dexmethylphenidate, in commercial quantities.

The relationship of dexmethylphenidate to levomethylphenidate appears to be somewhat different from the relationship of dextroamphetamine to levoamphetamine. In a series of experiments in children and naturally hyperkinetic dogs in the early 1970s, we found that both amphetamine isomers were significantly better than placebo for attention deficit hyperactivity disorder (known as minimal brain dysfunction at that time) and not significantly different from each other. Despite the similarity in behavioural effect, there were some subtle differences. Dextroamphetamine but not levoamphetamine improved visual-motor performance on the Bender Gestalt Test significantly more than did placebo. There was a nonsignificant tendency for the levo- isomer to have a slower start and to build up effect over several days or weeks. Affective adverse effects seemed anecdotally less severe with the levo- isomer, with some parents commenting that the child seemed more spontaneous and natural than with the 'other' isomer (in a crossover design) even though behaviour was as good with either. Blindly judged clinical results were better for more children with dextroamphetamine, but some children had their best result from levoamphetamine, and a couple responded to levoamphetamine who did not respond satisfactorily to any other available stimulant.

In contrast to the amphetamine situation, dexmethylphenidate appears to 'have all the

action', with levomethylphenidate not significantly better than placebo, and with similar results from equimolar dexamethylphenidate and racemic methylphenidate, which implies that levomethylphenidate does nothing or little. This difference may arise from the fact that methylphenidate, in contrast to amphetamine, is mainly metabolised in the liver rather than being renally excreted as the parent compound. In any event, it appears in this preliminary view of the data that the development of dexamethylphenidate from racemic threo-methylphenidate may be a more important therapeutic contribution than the development of dextroamphetamine from racemic amphetamine. Now if it were just available in an extended-release preparation . . .

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